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Risk taking and impulsive behaviour: fundamental discoveries, theoretical perspectives and clinical implications

Anthony R. Isles¹, Catharine A. Winstanley² and Trevor Humby³

¹ MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Hadyn Ellis Building, Maindy Road, Cardiff CF24 4HQ, UK

² Department of Psychology, University of British Columbia, Vancouver Campus, 2136 West Mall, British Columbia, Canada V6T 1Z4

³ School of Psychology, Cardiff University, Tower Building, 70 Park Place, Cardiff CF10 3AT, UK

Our willingness to take risks, our ability to wait or the speed with which to make decisions are central features of our personality. However, it is now recognized that impulsive and risk-taking behaviours are not a unitary construct, and different aspects can be both psychologically and neurally dissociated. The range of neurochemicals and brain systems that govern these behaviours is extensive, and this may be a contributing factor to the phenotypic range seen in the human population. However, this variety can also be pathological as extremes in risk-taking and impulsive behaviours are characteristics of many neuropsychiatric and indeed neurodegenerative disorders. This spans obsessive–compulsive disorder, where behaviour becomes ridged and non-spontaneous, to the nonsensical risk-taking seen in gambling and drug taking. This article is part of the theme issue ‘Risk taking and impulsive behaviour: fundamental discoveries, theoretical perspectives and clinical implications’.

1. Introduction

...our impulses are too strong for our judgement sometimes

– Thomas Hardy, *Tess of the D’Urbervilles*

How we respond in the face of a changing social and/or non-social environment is fundamental to human personality, and is an important facet of all animal behaviour. Underpinning this response is our willingness to take risks, our ability to wait or the speed with which we make decisions. At face value, risk-taking behaviour and impulsive behaviour are one and the same. However, research over a number of decades has established not only that risk taking and impulsivity can be dissociated, in terms of delay discounting for example [1,2], but that impulsivity itself is not a unitary construct and that a number of distinct facets are behaviourally dissociable [3–5]. More recent research has demonstrated that these are not simply descriptive distinctions, as we now know that discrete aspects of impulsive behaviour are mediated by different brain circuitries and neurochemistries [6,7], and that variations in these different forms of impulsive behaviour often do not correlate [8]. Moreover, a large range of psychiatric disorders, spanning obsessive–compulsive disorder, where behaviour becomes ridged and non-spontaneous, to the nonsensical risk-taking seen in gambling and drug taking, are classified as having an impulsive component.

Yet, these too present with different patterns of impulsive behavioural abnormalities [9–11], leading to distinct therapeutic strategies for different impulse control disorders [12].

Our aim, when compiling this Theme Issue, was to broadly explore impulsive and risk-taking behaviour. Collectively, the papers discuss the distinctions between discrete behaviours, the basic neural mechanisms and clinical conditions where abnormal risk-taking or impulsive behaviour is a feature. Additionally, a number of papers also consider the theories relating to how risk-taking and impulsive behaviour is generated within the brain, and how it may have developed over evolutionary time. Nevertheless, one aspect that is not covered specifically, in any great detail, in this Theme Issue is the genetic contribution to impulsive and risk-taking behaviours, despite the fact there are a great many studies linking single genes with aspects of impulsive behaviour and risk-taking. These include numerous rodent studies where the expression of a key candidate gene has been manipulated resulting in changes in impulsive and/or risk-taking behaviours [13–17], and even rare mutations in human families that link single genes to impulsive, risky or violent behaviour [18,19]. However, more general analyses of genetic variation and/or heritability are limited to a handful of rodent experiments [20–23] and twin studies in humans [24]. Moreover, convincing examples of hypothesis-free genome-wide studies of risk-taking and impulsive behaviour are limited. A recent genome-wide association study (GWAS) of delay discounting performance with 23 217 participants identified only one genome-wide significant single-nucleotide polymorphism [25]. Although located in a convincing target associated with the serotonin system (GPM6B), this is obviously a disappointing return.

The reason for this is probably because of the issue outlined above, and explored in greater detail by a number of papers in this special issue, which is that impulsivity and risk-taking behaviours represent many distinct constructs that interact in a number of complex ways. This is in contrast to simpler measures, such as height and body-mass index (BMI), in which GWAS studies have produced hundreds of genetic associations [26]. It is probably no surprise that the only really successful genome-wide study thus far has used an operational measure (delay discounting) rather than a broader definition of ‘choice impulsivity’ [25]. As a consequence, at present it is not possible to provide a cohesive and over-arching analysis of how genetic variation contributes to risk-taking and impulsive behaviours, in the same way that pathway analysis of GWAS data has generated novel insights into the biology of schizophrenia [27,28] and Alzheimer’s disease [29] for instance.

2. Overview of theme issue

As indicated above, this Theme Issue discusses many aspects of impulsive behaviour and risk-taking, bringing together basic researchers examining the mechanisms underpinning these behaviours, clinicians highlighting how these behaviours differentially impact on a range of conditions, and theorists discussing how brain systems may produce these behaviours and/or how they have developed over evolutionary time. Broadly the papers are grouped in this manner, although, of course, they all touch upon clinical conditions where impulsive or risk-taking behaviour goes awry.

In the first paper, Rosenbaum et al. [30] provide an overview of risky and impulsive choice behaviour, with particular emphasis on how these change over the course of development

and maturity. The next two papers form a pair, as both examine the conflict between choice of immediate but uncertain food rewards over delayed but certain food rewards. Stokes et al. [31] explore how this phenomenon varies in people in relation to BMI, and following exposure to food cues, such as food aroma. These findings have implications for behaviours that contribute to the rise in obesity in environments where food is readily available. Humby et al. [32] then describe the development of a touch-screen-based test of this same behaviour in mice. Using a behavioural pharmacology approach, they show that the choice of immediate but uncertain rewards in this task is sensitive to manipulations of 5HT_{2CR}, a key receptor mediating the effects of serotonin on both impulse control [33–35], and appetite [36,37].

Also addressing the psychology of conflict over choices, Studer et al. [38] explore whether precommitment strategies can aid individuals to achieve effort-requiring goals. The authors used two tasks, one where the choice was between a zero effort, small reward option and an increasing effort, large reward option (effort task); and one where the choice was between an immediate small reward option and an increasingly delayed, large reward option (delay task). The precommitment strategy involved choosing to remove the zero-effort or immediate reward option completely, and instead committing to the increasing effort, higher reward option in the effort task or the increasingly delayed, higher reward option in the delay task. In both the effort and delay tasks, where precommitment was chosen in trials, participants improved their rates of obtaining the larger reward. In addition, the authors used computational models of the choice behaviour to demonstrate that participants used precommitment to optimize their choice of the larger (but more effortful- or delayed-) reward by eliminating opportunity costs (i.e. as a self-motivational measure), rather than to prevent anticipated failures (i.e. as a self-regulatory measure). These data have obvious practical implications, and suggest the use of precommitment schemes in exercise and rehabilitation interventions.

Dalley & Ersche [39] dig more deeply into the neurobiology of one aspect of impulsivity, namely waiting impulsivity. Reviewing both animal and human studies, they detail the brain systems and neurotransmitters involved in mediating the ability to withhold a prepotent response until required. In addition to focusing on the fundamental mechanisms, this article links nicely with the next grouping of papers, more focused on clinical aspects. Specifically, Dalley & Ersche argue the importance of waiting impulsivity as a dimensional trait determining the predisposition to disorders of incentive motivation, particularly drug addiction. Moreover, they highlight the role of the serotonin system in the development of compulsive drug taking.

The relationship between impulsivity and drug addiction is explored further by Vassileva & Conrod [40] and Leeman et al. [41]. Vassileva focuses on how treatments could be directed at addressing domains of impulsivity as a novel clinical intervention for substance use disorders. Leeman et al. extend the role of impulsivity in addiction to include sexual tendencies in the light of the inclusion of compulsive sexual behaviour in the most recent edition of the International Classification of Diseases. Their systematic review supports the idea of a role for abnormal impulsivity as a precipitating factor or a consequence of addictive and/or sexual behaviours, but highlights gaps in the literature that need to be addressed with further, focused research.

The next two review articles broaden the discussion of impulsivity and risk-taking in the clinical context to include psychiatric disorders more generally. Lijffijt et al. [42] specifically focus on suicidality in bipolar disorder. They argue that the interaction between premorbid impulsivity and behavioural sensitization (in this case, the failure to reduce arousal in response to salient stimuli) can lead to a progression of psychiatric disorders. Lopez-Guzman et al. [43] discuss the interaction between choice impulsivity, as measured by delay discounting, and risk aversion. Although behaviourally and neurally distinct, the authors discuss the mathematical relationship between these two constructs, and in particular how operational measures of choice impulsivity often fail to take account of attitude to risk. They argue that this relationship may change in a complex manner, but nevertheless be key to understanding measures of choice impulsivity across a range of psychiatric disorders.

The remaining articles in this Theme Issue are more theoretical. Hertwig et al. [44] maintain that different approaches that have been developed to measure risk preference in behavioural sciences and economics have led to 'gaps' in our understanding of how stable risk preference is. They argue that the self-report measures, used in the behavioural sciences, show a higher degree of convergent validity and temporal stability than the behavioural measures typically used to study economic choice. Although possibly a controversial position, Hertwig et al. suggest that future research needs to address these gaps to test their predictive validity for economic and health consequences. Also approaching the topic of risk taking from an economic perspective, Bossaerts et al. [45] reason that current theories of decision-making, which model uncertainty about decision options using the tools of probability theory, may not be effective. They argue that in many situations, models, such as the Savage framework, are computationally intractable and, in situations in which computational complexity is high, ineffective in representing uncertainty. The authors conclude that new theories of decision-making, plausible from both a computational perspective and a biological perspective, are required from a scientific perspective and a public policy perspective.

The final two papers place impulsive behaviour and risk-taking in an evolutionary context. Hayden [46] takes a wide-ranging look at the issue of why impulsive and riskbased decisions appear to be sub-optimal (i.e. that choices do not maximize economical potential). Reasoning that the neural origins of self-control are primarily cognitive, Hayden also suggests that a more objective view tells us that although suboptimal choice is, on the face of it, a flaw, it is universal and is the product (or by-product?) of success over evolutionary time, therefore presumably is optimal in terms of biological function. Wilkins and Bhattacharya provide the theoretical basis for one possible contributing factor to why humans and animals may not appear optimal in their risk-taking and impulsive choices. Here, however, the focus is not on the psychological or behavioural level, but at the level of the gene. Specifically, they argue that the difference in reproductive variance between males and females—in many populations, male reproductive success is limited by access to females, whereas female reproductive success is mainly limited by physiology—can lead to differences in the 'willingness' of genes to be exposed to risk in the next generation. In particular, this has connotations for imprinted genes, a sub-set of mammalian genes that are differentially marked in a parent-of-origin-specific manner leading to monoallelic expression from one parental copy of the gene only. In the population scenario described

above, the suggestion is that paternally expressed imprinted genes would broadly act to reduce risk-taking, whereas maternally expressed imprinted genes would be more tolerant of risk-taking due to their exposure to different rates of the reproductive variance in the previous generation. Indeed, recent work examining knockout mouse models of two imprinted genes, *Nesp* and *Grb10*, provides broad empirical support for this idea [13,14]. It is easy to see how such a genetic tug-of-war may produce impulsive or risk-taking behaviour that appears sub-optimal.

3. Conclusion

Our aim is that the wide-ranging articles in this issue place our current understanding of risk-taking and impulsive behaviours in context. Nevertheless, what is abundantly clear is that there is still much work to be done in this field, at all levels of understanding. However, in bringing together a collection of papers that touch upon the basic and clinical science, and theoretical ideas, we hope this special issue will stimulate more research, but particularly cross-discipline research, into risk-taking and impulsive behaviours.

References

1. Holt DD, Green L, Myerson J. 2003 Is discounting impulsive? Evidence from temporal and probability discounting in gambling and non-gambling college students. *Behav. Process* 64, 355–367. (doi:10. 1016/S0376 6357(03)00141-4)
2. Green L, Myerson J. 1996 Exponential versus hyperbolic discounting of delayed outcomes: risk and waiting time. *Am. Zool.* 36, 496–505. (doi:10.1093/icb/36.4.496)
3. Bari A, Robbins TW. 2013 Inhibition and impulsivity: behavioral and neural basis of response control. *Prog. Neurobiol.* 108, 44–79. (doi:10.1016/j. pneurobio.2013.06.005)
4. Evenden JL. 1999 Varieties of impulsivity. *Psychopharmacology (Berl.)* 146, 348–361. (doi:10. 1007/PL00005481)
5. Humby T, Wilkinson LS. 2011 Assaying dissociable elements of behavioural inhibition and impulsivity: translational utility of animal models. *Curr. Opin Pharmacol.* 11, 534–539. (doi:10.1016/j.coph.2011. 06.006)
6. Talpos JC, Wilkinson LS, Robbins TW. 2006 A comparison of multiple 5-HT receptors in two tasks measuring impulsivity. *J. Psychopharmacol.* 20, 47–58. (doi:10.1177/0269881105056639)
7. Winstanley CA, Dalley JW, Theobald DE, Robbins TW. 2004 Fractionating impulsivity: contrasting effects of central 5-HT depletion on different measures of impulsive behavior. *Neuropsychopharmacology* 29, 1331–1343. (doi:10.1038/sj.npp.1300434)
8. Broos N et al. 2012 The relationship between impulsive choice and impulsive action: a crossspecies translational study. *PLoS ONE* 7, e36781. (doi:10.1371/journal.pone.0036781)
9. Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD. 2012 Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends Cogn. Sci.* 16, 81–91. (doi:10. 1016/j.tics.2011.11.009)
10. Swann AC, Lijffijt M, Lane SD, Steinberg JL, Moeller FG. 2009 Trait impulsivity and response inhibition in antisocial personality disorder. *J. Psychiatr. Res.* 43, 1057–1063. (doi:10.1016/j.jpsychires.2009.03.003)
11. Winstanley CA, Eagle DM, Robbins TW. 2006 Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. *Clin. Psychol. Rev.* 26, 379–395. (doi:10. 1016/j.cpr.2006.01.001)
12. Eagle DM, Bari A, Robbins TW. 2008 The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/ no-go tasks. *Psychopharmacology (Berl.)* 199, 439–456. (doi:10.1007/s00213-008-1127-6)
13. Dent CL, Humby T, Lewis K, Ward A, Fischer-Colbrie R, Wilkins LS, Wilkins JF, Isles AR. 2018 Impulsive choice in mice lacking paternal expression of *Grb10* suggests intragenomic conflict in behavior. *Genetics* 209, 233–239. (doi:10.1534/genetics.118.300898)
14. Dent CL, Humby T, Lewis K, Plagge A, Fischer-Colbrie R, Wilkins JF, Wilkinson LS, Isles AR. 2016 Impulsive choices in mice lacking imprinted *Nesp55*. *Genes Brain Behav.* 15, 693–701. (doi:10.1111/gbb. 12316)

15. Pena-Oliver Y, Sanchez-Roige S, Stephens DN, Ripley TL. 2014 Alpha-synuclein deletion decreases motor impulsivity but does not affect risky decision making in a mouse Gambling Task. *Psychopharmacology (Berl.)* 231, 2493–2506. (doi:10.1007/s00213-013-3416-y)
16. Doe CM, Relkovic D, Garfield AS, Dalley JW, Theobald DE, Humby T, Wilkinson LS, Isles AR. 2009 Loss of the imprinted snoRNA mbii-52 leads to increased 5htr2c pre-RNA editing and altered 5HT2CR-mediated behaviour. *Hum. Mol. Genet.* 18, 2140–2148. (doi:10.1093/hmg/ddp137)
17. Brunner D, Hen R. 1997 Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice. *Ann. N Y Acad. Sci.* 836, 81–105. (doi:10.1111/j.1749-6632.1997.tb52356.x)
18. Bevilacqua L et al. 2010 A population-specific HTR2B stop codon predisposes to severe impulsivity. *Nature* 468, 1061–1066. (doi:10.1038/nature09629)
19. Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA. 1993 Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science* 262, 578–580. (doi:10.1126/science.8211186)
20. Pinkston JW, Lamb RJ. 2011 Delay discounting in C57BL/6 J and DBA/2 J mice: adolescent-limited and life-persistent patterns of impulsivity. *Behav. Neurosci.* 125, 194–201. (doi:10.1037/a0022919)
21. Patel S, Stolerman IP, Asherson P, Sluyter F. 2006 Attentional performance of C57BL/6 and DBA/2 mice in the 5-choice serial reaction time task. *Behav. Brain Res.* 170, 197–203. (doi:10.1016/j.bbr.2006.02.019)
22. Helms CM, Reeves JM, Mitchell SH. 2006 Impact of strain and D-amphetamine on impulsivity (delay discounting) in inbred mice. *Psychopharmacology (Berl.)* 188, 144–151. (doi:10.1007/s00213-006-0478-0)
23. Isles AR, Humby T, Walters E, Wilkinson LS. 2004 Common genetic effects on variation in impulsivity and activity in mice. *J. Neurosci.* 24, 6733–6740. (doi:10.1523/JNEUROSCI.1650-04.2004)
24. Anokhin AP, Grant JD, Mulligan RC, Heath AC. 2015 The genetics of impulsivity: evidence for the heritability of delay discounting. *Biol. Psychiatry* 77, 887–894. (doi:10.1016/j.biopsych.2014.10.022)
25. Sanchez-Roige S et al. 2018 Genome-wide association study of delay discounting in 23,217 adult research participants of European ancestry. *Nat. Neurosci.* 21, 16–18. (doi:10.1038/s41593-017-0032-x)
26. Robinson MR et al. 2015 Population genetic differentiation of height and body mass index across Europe. *Nat. Genet.* 47, 1357–1362. (doi:10.1038/ng.3401)
27. Ursini G et al. 2018 Convergence of placenta biology and genetic risk for schizophrenia. *Nat. Med.* 24, 792–801. (doi:10.1038/s41591-018-0021-y)
28. Schizophrenia Working Group of the Psychiatric Genomics Consortium. 2014 Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511, 421–427. (doi:10.1038/nature13595)
29. Jones L et al. 2010 Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. *PLoS ONE* 5, e13950. (doi:10.1371/journal.pone.0013950)
30. Rosenbaum GM, Hartley CA. 2019 Developmental perspectives on risky and impulsive choice. *Phil. Trans. R. Soc. B* 374, 20180133. (doi:10.1098/rstb.2018.0133)
31. Stokes L-JG, Davies A, Lattimore P, Winstanley C, Rogers RD. 2019 Exploring preferences for variable delays over fixed delays to high-value food rewards as a model of food-seeking behaviours in humans. *Phil. Trans. R. Soc. B* 374, 20180141. (doi:10.1098/rstb.2018.0141)
32. Humby T, Patel Y, Carter J, Stokes L-JG, Rogers RD, Wilkinson LS. 2019 Feeding behaviour, risksensitivity and response control: effects of 5-HT2C receptor manipulations. *Phil. Trans. R. Soc. B* 374, 20180144. (doi:10.1098/rstb.2018.0144)
33. Humby T, Eddy JB, Good MA, Reichelt AC, Wilkinson LS. 2013 A novel translational assay of response inhibition and impulsivity: effects of prefrontal cortex lesions, drugs used in ADHD, and serotonin 2C receptor antagonism. *Neuropsychopharmacology* 38, 2150–2159. (doi:10.1038/npp.2013.112)
34. Fletcher PJ, Tampakeras M, Sinyard J, Higgins GA. 2007 Opposing effects of 5-HT2A and 5-HT2C receptor antagonists in the rat and mouse on premature responding in the five-choice serial reaction time test. *Psychopharmacology (Berl.)* 195, 223–234. (doi:10.1007/s00213-007-0891-z)
35. Winstanley CA, Theobald DE, Dalley JW, Glennon JC, Robbins TW. 2004 5-HT2A and 5-HT2C receptor antagonists have opposing effects on a measure of impulsivity: interactions with global 5-HT depletion. *Psychopharmacology (Berl.)* 176, 376–385. (doi:10.1007/s00213-004-1884-9)
36. Lam DD, Przydzial MJ, Ridley SH, Yeo GS, Rochford JJ, O'Rahilly S, Heisler LK. 2008 Serotonin 5-HT2C receptor agonist promotes hypophagia via downstream activation of melanocortin 4 receptors. *Endocrinology* 149, 1323–1328. (doi:10.1210/en.2007-1321)
37. Somerville EM, Horwood JM, Lee MD, Kennett GA, Clifton PG. 2007 5-HT(2C) receptor activation inhibits appetitive and consummatory components of feeding and increases brain c-fos immunoreactivity in mice. *Eur. J. Neurosci.* 25, 3115–3124. (doi:10.1111/j.1460-9568.2007.05567.x)

38. Studer B, Koch C, Knecht S, Kalenscher T. 2019 Conquering the inner couch potato: precommitment is an effective strategy to enhance motivation for effortful actions. *Phil. Trans. R. Soc. B* 374, 20180131. (doi:10.1098/rstb.2018.0131)
39. Dalley JW, Ersche KD. 2019 Neural circuitry and mechanisms of waiting impulsivity: relevance to addiction. *Phil. Trans. R. Soc. B* 374, 20180145. (doi:10.1098/rstb.2018.0145)
40. Vassileva J, Conrod PJ. 2019 Impulsivities and addictions: a multidimensional integrative framework informing assessment and interventions for substance use disorders. *Phil. Trans. R. Soc. B* 374, 20180137. (doi:10.1098/rstb.2018.0137)
41. Leeman RF, Rowland BHP, Gebru NM, Potenza MN. 2019 Relationships among impulsive, addictive and sexual tendencies and behaviours: a systematic review of experimental and prospective studies in humans. *Phil. Trans. R. Soc. B* 374, 20180129. (doi:10.1098/rstb.2018.0129)
42. Lijffijt M, O'Brien B, Salas R, Mathew SJ, Swann AC. 2019 Interactions of immediate and long-term action regulation in the course and complications of bipolar disorder. *Phil. Trans. R. Soc. B* 374, 20180132. (doi:10.1098/rstb.2018.0132)
43. Lopez-Guzman S, Konova AB, Glimcher PW. 2019 Computational psychiatry of impulsivity and risk: how risk and time preferences interact in health and disease. *Phil. Trans. R. Soc. B* 374, 20180135. (doi:10.1098/rstb.2018.0135)
44. Hertwig R, Wulff DU, Mata R. 2019 Three gaps and what they may mean for risk preference. *Phil. Trans. R. Soc. B* 374, 20180140. (doi:10.1098/rstb.2018.0140)
45. Bossaerts P, Yadav N, Murawski C. 2019 Uncertainty and computational complexity. *Phil. Trans. R. Soc. B* 374, 20180138. (doi:10.1098/rstb.2018.0138)
46. Hayden BY. 2019 Why has evolution not selected for perfect self-control? *Phil. Trans. R. Soc. B* 374, 20180139. (doi:10.1098/rstb.2018.0139)